REMARKS

Reconsideration of the rejections set forth in the Office action mailed March 12, 2002 is respectfully requested. Claims 1-8 are currently under examination.

I. Amendments

The first paragraph of the specification has been amended to add a reference to the parent application.

II. Allowable Subject Matter

Claim 8 has been allowed.

III. Drawings

Enclosed is a complete set of formal drawings, to replace the previous set of drawings.

IV. Rejections under 35 U.S.C. §103

The previous rejection of claims 1-6 under 35 U.S.C. §103, as being unpatentable over Lamond *et al.* (*FEBS Letters* **325**(1,2):123-27, 1993), Kandimalla *et al.* (*Nucleosides & Nucleotides* **14**(3-5):1031-35, 1995), and Baracchini *et al.* (U.S. Patent No. 5,801,154), has been maintained.

The rejection is respectfully traversed in light of the following remarks.

A. The Invention

The applicant's invention, as embodied in generic claim 1, is directed to a chimeric oligonucleotide having the formula 5'–W–X^1–Y–X^2–Z–3', where W represents a 5'-O-alkyl nucleotide, each of X^1 and X^2 represents a block of seven to twelve phosphodiester-linked 2'-O-alkyl ribonucleotides, Y represents a block of five to twelve phosphorothioate-linked deoxyribonucleotides, and Z represents a blocking group effective to block nuclease activity at the 3' end of the oligonucleotide.

As shown in the specification at, for example, Figs. 3-4 and Table 1, oligonucleotides having the claimed structure produced reductions in target mRNA levels, in B16 and HT1080 cells, of 80% or more. The oligos were effective with the transfection agent L1, shown in Fig. 2, as well

as with a commercially available cytofectin transfection agent (see Fig. 4).

B. The Cited Art

As discussed in the previous response, Lamond *et al.* discloses a homopolymeric modified oligonucleotide, having all phosphodiester-linked 2'-O-alkyl ribonucleotide subunits, and Kandimalla discloses an oligomer having a two-block structure, ie. a sequence of methylphosphonate-linked 2'-O-methyl ribonucleosides linked to a sequence of native DNA. Neither reference describes or suggests chimeric oligonucleotides having phosphorothioate linkages, or having the "winged" structure presently claimed.

Baracchini *et al.* is the only reference of those cited which discloses a "winged" chimeric oligonucleotide. As discussed in the previous response, the disclosure of this reference, at columns 12-13 and Table 4, with reference to several figures, describes a trend of less antisense activity as the number of 2'-alkylated ribonucleotide subunits in the "wings" of the chimeric structure is increased, from 4 to 6 (compound 13039 vs. 13041). Decreases in activity were also seen when all-phosphorothioate oligonucleotides were modified to those having "wings" of phosphodiester-linked nucleotides (13039 vs 13038 and 13041 vs. 13040, respectively.)

C. Analysis

The Examiner has not made out a proper prima facie case of obviousness. The cited references describe oligomers having completely different linkage types and block patterns, and thus provide no motivation for combination, nor any guidance as to how they could or should be combined.

In the Office Action, the Examiner stated that "the efficacy of an antisense oligonucleotide is dependent on the structure of its mRNA target, and the accessibility of its target sequence". In addition, the Examiner stated that one "would not accept on its face that the behavior of the modified antisense oligonucleotides of Baracchini et al. would necessarily predict the efficacy of all antisense oligonucleotides having the same or similar structure and modification as those disclosed". In response, the applicants note that the four differently modified oligonucleotides of Baracchini described above have the same sequence and therefore the same mRNA target, and one should therefore be able to draw some conclusions about the effect of the described structural modifications on the activity of the compounds. In applying such conclusions to other modified oligonucleotides, one of skill in the art would, if anything, expect the effects to follow the trend

shown in the reference (that is, to favor oligonucleotides having fewer flanking ribonucleotide subunits and/or a greater proportion of phosphorothioate linkages) rather than to reverse the trend. To do otherwise would simply discount the teachings of the reference.

In view of the fact that the compounds of Baracchini that include "wings" are not efficacious, there would certainly be no reasonable expectation of success in modifying the teachings of the reference along the lines of the invention. (Alternatively, if one followed the Examiner's reasoning, and concluded that the teachings of the reference held no predictive ability, then it could certainly provide no expectation of success.)

V. Further Rejections under 35 U.S.C. §103

The previous rejection of claim 7 under 35 U.S.C. §103, as being unpatentable over Lamond *et al.*, Kandimalla *et al.*, and Baracchini *et al.*, above, in view of Rosch *et al.* (U.S. Patent No. 5,750,669), has been maintained.

The rejection is respectfully traversed in light of the following remarks.

A. The Invention

The applicant's invention, as embodied in claim 7, is directed to the composition of generic claim 1, comprising a chimeric oligonucleotide as described above, wherein the 3' terminal group Z is a 3'-to-3' linked nucleotide.

B. The Cited Art

Lamond *et al.*, Kandimalla *et al.*, and Baracchini *et al.* are discussed above. Further to this discussion, none of these references discloses or suggests a 3'-to-3' terminal nucleotide.

Rosch *et al.* describes the benefits of a terminal 3'-3' and/or 5'-5' internucleotide linkage in increasing stability of oligonucleotides against nucleases. As noted in the previous response, the reference discusses problems encountered with modified-backbone oligonucleotides designed to increase nuclease stability. Such problems included, for example, lack of specificity and the "chirality problem" in the widely used thiophosphate oligomers (another name for phosphorothioates) (column 2, lines 20-30).

In contrast, the authors found that "this minimal structural modification" (i.e., the 3'-3' and/or 5'-5' terminal internucleotide linkage) "suffices to stabilize such components against nuclease degradation" (column 5, lines 21-23). Further, this "only slight structural modification

results in a hybridization behavior which is almost identical to that of the biological oligonucleotides" (column 5, lines 24-26).

Because Roche *et al.* discusses the problems associated with modified backbone linkages (including phosphorothioates), and touts the benefits of modifying only the terminal groups of the oligonucleotide to achieve nuclease stability, the reference would not motivate one to prepare any kind of backbone-modified oligonucleotide, particularly one containing phosphorothioate linkages.

In view of the foregoing, the applicants respectfully request that the rejections under 35 U.S.C. §103 be withdrawn.

VI. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

No further fees are believed necessary with this communication. However, the Commissioner is hereby authorized and requested to charge any deficiency in fees herein, or credit any overpayment, to Deposit Account No. 50-2207.

Respectfully submitted,

Date: 7-12-02

LeeAnn Gorthey
Registration No. 37,337
Phone: (650) 838-4403
Fax: (650) 838-4350

Correspondence Address:
Chiron Corporation
Intellectual Property R440
P.O. Box 8097
Emeryville CA 94662-8097

Amendments to specification
U.S. Serial No. 09/826,519

Please amend the paragraph at page 1, lines 5-7, as follows:

This application is a divisional of U.S. serial no. 09/648,254, filed August 25, 2000, which claims priority to U.S. provisional application serial no. 60/151,246, filed August 27, 1999, both of which [is] are hereby incorporated by reference in [its] their entirety and for all purposes.